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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/459,573	12/13/1999	VITALIY ARKADIEVICH LIVSHITS	0010-1066	1340

7590 03/19/2004

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/459,573	LIVSHITS ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/8/02*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 45-53 are pending.

Applicant's amendment of claim 45-48 in a communication filed on 12/22/2003 is acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 4/8/2002 is acknowledged. Reference "AW" has not been considered since no year or author is associated with said reference. The remainder of the submission is in compliance with the provisions of 37 CFR 1.97 and is being considered by the Examiner.

Claim Objections

2. Claim 46 is objected to due to the recitation of "a cell". While a bacterium is a cell, for clarity and consistency, it is suggested that the term be replaced with "the bacterium" since this is the term used throughout the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 45-53 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s),

at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in an Office Action mailed 7/25/2003.

5. Applicants argue that Examples 3 and 7 clearly demonstrate the effect of amplification of 3 different plasmids on L-glutamic acid production and L-proline production, respectively. According to Applicants, expression of the YahN gene in such plasmids clearly has an effect in the production of glutamic acid and proline production as seen in Tables 2 and 7, respectively. It is Applicant's contention that Examples 3 and 7 clearly contradict the Examiner's assertion regarding the lack of disclosure of proline or glutamic acid excreting proteins since these examples shows that the protein encoded by the YahN gene enables excretion of L-glutamic acid and L-proline. Applicants also note that production of glutamic acid and proline does not necessarily lead to the presence of a single proline or glutamic acid excreting protein and that the three amino acids are inherently produced in the medium of Examples 3 and 7. Applicants further submit that amino acid excreting genes and their corresponding proteins are described and identified by their SEQ ID NO: in pages 8-9 and that SEQ ID NO: 10 is clearly described as a protein capable of the activity of enabling excretion of L-glutamic acid, L-lysine and L-proline. Applicants argue that one of skill in the art would be able upon the conditions recited in the claim and the description in the specification to determine which polynucleotides would encode proteins having the same activity as that of SEQ ID NO: 10.

6. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. The Examiner agrees with Applicants regarding the effect of expressing the YahN gene in the increased production of glutamic acid, lysine and proline. The Examiner also acknowledges the teachings of the specification as shown in Examples 3 and 7 as well as the disclosure of the structure of the YahN gene and the corresponding protein. However, the Examiner disagrees with Applicant's contention that the teachings of the specification clearly demonstrate that there is adequate description of a polynucleotide hybridizing to the YahN gene wherein said polynucleotide encodes a proline or a glutamic

acid excreting protein. Examples 3 and 7 demonstrate that there is increased production of lysine, glutamic acid and proline when the YahN gene is expressed at levels higher than those in wild-type strains of E. coli, however nowhere in the specification there is corroboration or experimental evidence that the increased production of glutamic acid and proline is due to an increased transport of these amino acids to the medium by the polypeptide of SEQ ID NO: 10. While there is additional evidence by Blattner and Vrljic (cited in a previous Office Action) to support the argument that the polypeptide of SEQ ID NO: 10 is indeed a lysine transport protein, there is no experimental evidence or additional evidence which shows that the polypeptide of SEQ ID NO: 10 is indeed a transport protein for proline or glutamic acid. Neither Blattner nor Vrljic teach or suggest the polypeptide of SEQ ID NO: 10 to be a transport protein for proline or glutamic acid. The increased production in proline and glutamic acid in Examples 3 and 7 may not be due to the increased transport of these amino acids by the polypeptide of SEQ ID NO: 10 but rather due to the dependency among the different biosynthetic pathways in a cell. As known in the art, the biosynthetic pathways of amino acids are interconnected such that an increase in the synthesis of one may result in the increase of others. It is also noted that the specification while disclosing the structure of the polypeptide of SEQ ID NO: 10, fails to disclose which are the structural elements in a polypeptide encoded by a polynucleotide which hybridizes under the recited conditions to the polynucleotide of SEQ ID NO: 9 that are characteristic of glutamic acid or proline excreting proteins. Therefore, Applicants have not provided adequate description of all the polynucleotides required to practice the claimed method.

7. It is noted that limiting the L-amino acid excreting activity to L-lysine in step (B) may overcome the instant rejection.

8. Claims 45-53 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing L-proline, L-lysine and L-glutamic acid by cultivating an

Escherichia cell which has been modified such that (1) the copy number of a DNA encoding the polypeptide of SEQ ID NO: 10 or a DNA which hybridizes to the polynucleotide of SEQ ID NO: 9 at 60 C, 1xSSC and 0.1%SDS and encodes a protein with lysine transport activity is increased or (2) the expression of said DNA is not under the control of its native promoter but it is under the control of any strong promoter, does not reasonably provide enablement for said method wherein the Escherichia cell has been modified such that (1) the copy number of a DNA which hybridizes to the polynucleotide of SEQ ID NO: 9 and encodes any proline or any glutamic acid excreting protein is increased or (2) the expression of said DNA is not under the control of its native promoter but it is under the control of any strong promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length in an Office Action mailed 7/25/2003.

9. Applicants argue that the lack of enablement indicated by the Examiner is contradicted by the data presented in Examples 3 and 7. Furthermore, Applicants assert that the specification is clearly enabling for the amino acid excreting proteins which enable excretion of L-lysine, L-glutamic acid, and L-proline, particularly the YahN protein, for the reasons discussed above in regard to the written description rejection.

10. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. As indicated above, the teachings of the specification, such as the disclosure of SEQ ID NO: 9 and 10, as well as Examples 3 and 7 are not deemed sufficient for one of skill in the art to reasonably conclude that the increase in proline and glutamic acid production is due to increase transport of these amino acids to the medium by the polypeptide of SEQ ID NO: 10. See discussion above. Furthermore, as indicated previously, the specification fails to teach which are the critical structural elements in the polynucleotide of SEQ ID NO: 9 or the polypeptide of SEQ ID NO: 10 which are essential for a polynucleotide or a polypeptide to have proline or glutamic acid excreting function. While one could

argue that making the required polynucleotides is not undue experimentation since it will require the use of techniques known by the skilled artisan, it is noted that while making any number of polynucleotides may not be undue experimentation, testing an extremely large number of polynucleotides to determine which ones encode proline or glutamic acid excreting proteins is not routine experimentation. The skilled artisan would not test an infinite number of polynucleotides but would test only those polynucleotides more likely to encode the proteins with the desired function. As indicated in the previous Office Action, in the absence of additional evidence, one of skill in the art would not expect an increase in glutamic acid or proline production by increasing the amount of a lysine transport protein or an increase in glutamic acid or proline production due to increase transport of said amino acids by the polypeptide of SEQ ID NO: 10. Neither Blattner nor Vrljic teach or suggest that a lysine transport protein would also transport glutamic acid or proline. Therefore, in view of the information provided, the lack of relevant examples, the lack of knowledge about the critical elements required to display the desired function, and the teachings of the art regarding the unpredictability of enhancing the production of one amino acid by increased expression of another amino acid excreting protein, one of skill in the art cannot reasonably conclude that the specification fully enables the full scope of the claimed invention.

11. It is noted that limiting the L-amino acid excreting activity to L-lysine in step (B) may overcome the instant rejection.

Claim Rejections - 35 USC § 103

12. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

13. Claims 45-51 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Blattner et al. (GenBank accession number P75693, November 1, 1997) in view of Vrljic et al. (Mol. Microbiol.

22:815-826, 1996) and Kojima et al. (U.S. Patent No. 6040160, 102(e) date 5/29/1996). This rejection has been discussed at length in an Office Action mailed 7/25/2003.

14. Applicants argue that the teachings of Blattner are insufficient and that the remaining references do not render the claimed invention obvious. Applicants submit a reference by Vrljic et al. (J. Mol. Microbiol. Biotechnol. 1(2):327-336, November 1999) in support of the argument that the members of the lysE superfamily share little to no homology and that the functions of the different members of the family are different. Therefore, even if Blattner suggested that the polypeptide of SEQ ID NO: 10 is a lysE homolog, one of skill in the art would not have reasonably expected that YahN would have a function similar to that of LysE.

15. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. While the Examiner acknowledges the teachings of the reference submitted (Vrljic et al., 1999), it is noted that this reference also teaches that the members of the lysE superfamily are transmembrane solute translocators. Since Blattner et al. disclosed the polypeptide of SEQ ID NO: 10 as a lysE homolog of the C. glutamicum LysE protein, one of skill in the art would have expected the polypeptide of SEQ ID NO: 10 to be at the very least a transport protein which could be the counterpart of the C. glutamicum lysE protein. As such, one of skill in the art (1) would have been motivated to transform an E. coli cell to overexpress the polynucleotide of SEQ ID NO: 9 to produce L-lysine, and (2) would have had a reasonable expectation of success in view of the teachings of Vrljic et al. (1996) and Kojima et al. It is also noted that all that is required in the obviousness analysis is a reasonable expectation of success, which was present at the time the invention was made for the reasons already discussed. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

16. Claims 45-53 would be allowable if claim 45 is (1) limited to the production of proline and glutamic acid, and (2) limited to L-lysine excreting activity in step (B).

Conclusion

17. No claim is in condition for allowance.

18. Applicant's amendment of claims 45-48 necessitated the new ground(s) of rejection/objection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
March 9, 2004

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